

Guidance for Industry

The Use of Published Literature in Support of New Animal Drug Approval

DRAFT GUIDANCE

Guidance issued for comment purposes only.

This draft guidance is intended to provide specific advice regarding the use of published literature to support new animal drug approval.

This draft guidance represents our current thinking on this matter. It does not create or confer any rights for or on any person and does not operate to bind us or the public. You may use an alternative approach as long as it satisfies the requirements of the applicable statute and regulations.

Comments and suggestions regarding this draft document should be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket Number provided in the Federal Register notice announcing the availability of this draft guidance.

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THE USE OF PUBLISHED LITERATURE IN SUPPORT OF NEW ANIMAL DRUG APPROVAL

For approval of a new animal drug, section 512 of the Federal Food, Drug, and Cosmetic Act requires that adequate tests show whether or not the drug is safe and that there is substantial evidence of effectiveness. Substantial evidence is defined in section 512 as one or more adequate and well-controlled studies. Essential characteristics of adequate and well-controlled studies intended to demonstrate effectiveness are described in 21 CFR 314.117. To demonstrate that a study supporting an effectiveness claim is adequate and well-controlled, sponsors usually submit extensive documentation of study planning, protocol, conduct, and data handling to FDA, and all study documentation¹ is made available at the study sites. Similarly, to demonstrate that a study intended to support a finding that a new animal drug is safe is adequately designed and conducted, sponsors usually submit extensive documentation of study planning, protocol, conduct, and data handling to FDA, and all study documentation is made available at the study sites.

From a scientific standpoint, however, FDA recognizes that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, FDA is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This guidance discusses the factors that influence the extent of documentation needed.

For purposes of this document, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the raw data² and the original study-related records (e.g., drug accountability records) for the purpose of determining the validity of data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequately designed and controlled.

In practice, to achieve a high level of documentation, non-clinical studies supporting new animal

¹ Study documentation includes all records in any form (including documents, magnetic and optical records) describing methods and conduct of the study, factors affecting the study, and any actions taken. These records include, but are not limited to: protocol, raw data, reports, SOP's, reference materials, and specimens.

² Raw data includes any worksheets, calibration data, records, memoranda and notes of original observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, computer printouts, magnetic, electronic, or optical media, information recorded from automated instruments, and hand recorded data sheets. Facsimile transmissions and transcribed data are not considered raw data.

drug approval are ordinarily conducted in accordance with Good Laboratory Practices (GLPs); clinical studies supporting new animal drug approvals are ordinarily conducted in accordance with Good Target Animal Study Practices set out in CVM's Guidance for Industry 58, and should be conducted in accordance with any final guidance regarding Good Clinical Practice issued under the VICH³ process. Testing facilities are required under the GLP regulations at 21 CFR 58.35 to quality assure the integrity of a non-clinical study, and FDA routinely has access to raw data and records that confirm that quality assurance audits were performed. Sponsors are expected to routinely monitor all clinical study sites, and FDA routinely has access to the study documentation.

However, situations often arise in which studies that evaluate the safety or effectiveness of a drug product lack the full documentation described above. Under certain circumstances, it is possible for sponsors to rely on such studies to support the approval of a new animal drug, despite less than usual documentation. Some of those circumstances, particularly as they relate to the use of published literature, are described below.

Using Published Literature

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Because such studies are not specifically conducted to support new animal drug approval, experience has shown that such study reports do not always contain a complete or entirely accurate representation of study plans, conduct, and outcomes. Incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. In most instances, journal article peer reviewers only have access to limited data sets and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers.

The presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to support approval of a new animal drug. FDA's reliance on published literature to support approval of a new animal drug is more likely if FDA can obtain additional critical study details. Section I below describes additional information that, if available, would increase the likelihood that a study reported in published literature could be relied on to support approval of a new animal

³ "VICH" is the acronym for International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. The VICH is a trilateral program aimed at harmonizing the technical requirements for veterinary product registration.

drug. Section 2 describes factors that may make findings of safety or effectiveness sufficiently persuasive to permit reliance solely on published literature. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of published literature generally, whether alone or accompanied by other important information as discussed in Section 1.

Section 1. Submission of Published Literature in Conjunction with Other Important Information that Enhances the Reliability of the Data

Providing as many as possible of the following important pieces of information about a particular study reported in published literature increases the likelihood that the study can be relied on to support a new animal drug approval.

- a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study animal accrual or randomization.
- b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study.
- c. Randomization codes and documented study entry dates for the animals.
- d. Full accounting of all study animals, including identification of any animals with on-treatment data that have been omitted from analysis and the reasons for omissions, and an analysis of results using all animals with on-study data.
- e. Individual animal or herd source data for critical variables and pertinent baseline characteristics.
- f. Complete information for all deaths and drop-outs and details of any adverse event(s).
- g. Documentation of the characterization of the test substance.

Section 2. Submission of Published Literature Without Submission of Underlying Data

The following factors increase the possibility of reliance on published reports alone to support the approval of a new animal drug:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

- b. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment.
- c. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all animals.
- d. Robust results achieved by protocol-specified analyses that yield a conclusion of safety and effectiveness.
- e. Conduct of studies by investigators with properly documented operating procedures and a history of implementing such procedures effectively.

A sponsor should indicate as part of its submission of published literature, the specific issues which the published literature are intended to address. Section 512 of the Federal Food, Drug, and Cosmetic Act requires that a sponsor submit, as part of a new animal drug application (NADA), full reports of investigations which have been made to show whether or not a new animal drug is safe and effective for use. Thus, current regulations require that a sponsor provide as part of its NADA all information pertinent to an evaluation of safety and effectiveness of the new animal drug, including reports in scientific literature, both favorable and unfavorable. 21 CFR 514.1(b)(8)(iv).

Concern has been expressed in recent years that published studies represent a skewed subset of all existing information available on a particular subject. The likelihood that FDA will rely on published literature is enhanced when we have a balanced discussion both of the published studies that raise questions relating to the safety and effectiveness of the new animal drug, as well as the published studies that support a finding of safety and effectiveness.

Sponsors, including sponsors of new animal drugs intended for minor uses or intended for use in minor species, are encouraged to discuss with the Center for Veterinary Medicine the use of published literature in support of new animal drug approval.